Remarks

Applicants enclose four Replacement drawings, Figures 1-4. Original Figure 1 is now Table A, and original Figures 2 to 5 are now Figures 1 to 4, respectively. No new matter has been added.

Election/Restriction

Claims 5-18, 20-28, 37, 40-41 and 46-47 were withdrawn from consideration as being drawn to a non-elected invention. Claims 28 and 32-47 have been cancelled. Applicants have petitioned the Group Director for reconsideration of the Restriction Requirement as to the remaining claims. Pending a decision, these claims have been treated as under examination.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1, 2, 3, 4, 19, 29-31, 35-36, 38-39 and 41 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Legal Standard

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*See, e.g., Amgen v. Hoechst Marion Roussell* 314 F.3d 1313 (Fed. Cir. 2003; *Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d at 165, 42 USPQ2d at 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993);

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See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir.1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.* , 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir.1984). There is no requirement for examples.

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A proper analysis of the *Wands* factors shows that the claims satisfy the enablement requirement. The quantity of experimentation necessary for treating cachexia in a patient by administering an effective amount of an agent which reduces sympathetic nervous system activity is **not undue.** It is important to understand that that the claims are directed to the **treatment of weight loss** due to an underlying disease, **not** the disease itself. Applicants submit that a common mechanism (i.e. increased SNS activity) leads to cachexia in a number of patients with different diseases. Therefore, cachexia can be treated with drugs that are functionally-related by their ability to decrease SNS activity.

On page 27, line 25 to page 28, line 9, the specification describes how cachexia relates to sympathetic nervous system activity and refers to Table A and Figure 1 (original Figures 1 and 2), which demonstrate that patients with weight loss due to a number of diseases have elevated noradrenaline plasma levels (i.e. SNS activity) compared to controls. In addition, Figures 2 and 3 (original Figures 3 and 4) provide data showing increased aldosterone and angiotensin II levels, respectively, in cachectic subjects. Accordingly, the Applicants have found that cachectic patients with a range of underlying diseases show a similar hormonal profile, and have envisioned how to treat the weight loss with the agents listed on page page 4, line 10 to page 13, line 22.

These compounds are known agents (although not for the treatment of cachexia), with established mechanisms of action. All of these compounds affect sympathetic nervous system activity and are, therefore, related through this common action. It would be routine for one of

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skill in the art to select a suitable agent and a suitable dose for the treatment of cachexia based on the pharmacological profiles of these known agents.

The Examiner alleges that the Applicants have not shown whether higher doses of spironolactone are safe for a patient. Applicants enclose pages from Martindale, The Complete Drug Reference, 33rd edition, which teach that in the treatment of edema, spironolactone is usually given at an initial dose of 100 mg daily by mouth and subsequently adjusted as necessary. It goes on to say that some patients may require doses of up to 400 mg daily (see the section entitled "Uses and Administration" on page 974, third column). Therefore, this reference demonstrates that spironolactone is indeed safe at the doses described in the specification (12.5 to 300 mg/day, page 4, lines 14-15). Thus, the initially greater weight loss seen in the RALES study with 75 mg of spironolactone is entirely consistent with the diuretic activity of the drug.

Applicants enclose publications demonstrating the effects of other inhibitors of sympathetic nervous system activity on cachexia, further indicating that the claims are enabled.

Hryniewicz et al. *J. Card. Fail* 9(6): 464-468 (2003) shows a partial reversal of cardiac cachexia by b-adrenergic receptor blocker therapy. Coats et al. *Abstract No. 2071 from the Scientific Sessions 2001 of the American Heart Association* 104: II.437 (2001) reports prevention and reversal of cardiac cachexia by carvedilol (listed on page 5 of the specification as a b-receptor blocker). Hryniewicz et al. (2003) refers to Anker et al. American College of Cardiology 2003 Scientific Sessions (Abstract enclosed) (Reference 19), which reports

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prevention and reversal of cachexia by bisoprolol (listed on page 5 of the specification as a β-receptor blocker).

With respect to claims 35-36 and 38-39, the Examiner's rejection is moot since these claims have been cancelled.

It is clear from the amount of direction or guidance presented in the specification, the state of the prior art, the relative skill of those in the art, that one of ordinary skill in the art could use an agent which reduces sympathetic nervous system activity to treat weight loss due to underlying disease in a patient.

Claims 1, 2, 3, 4, 19, 35, 36, 38, 39, 41 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Legal Standard

The law has long allowed an applicant to claim all that he is entitled to, not forcing him to limit his claims to a specific example, if other means for achieving the same step would be known to those skilled in the art and not require undue experimentation. That is clearly the case here.

"There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed". *Wertheim*, 541 F.2d at 262, 191 USPQ at 96 (CCPA 1976).

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The written description requirement for a claimed genus may be satisfied through a sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or a disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

The Applicants have discovered that a common mechanism (i.e. increased SNS activity) leads to cachexia in a number of patients with different diseases. One of ordinary skill in the art has a thorough understanding of the sympathetic nervous system and would know how to select a suitable compound to reduce its activity. To limit the claims to the specific compounds listed in claim 4 would be completely improper. As stated above, a large number of compounds that reduce SNS activity and may be used to treat weight loss due to underlying disease are described on page 4, line 10 to page 8, line 6. On page 8, line to page 13, line 22, the specification further discloses publications in which many of the compounds are described in detail. Again, these compounds are well known (although not for the treatment of cachexia), and many have been used in humans. It would not be beyond the grasp of the skilled artisan to use these compounds, or any other compound that reduces SNS activity, to treat a patient with cachexia, even though the compounds may have different structures and biological targets.

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With respect to claims 35-36 and 38-39, the Examiner's rejection is moot since these claims have been cancelled.

The specification satisfies the written description requirement by disclosing a sufficient description of a representative number of species by functional characteristics (i.e. effect on SNS activity) coupled with a known or a disclosed correlation between function and mechanism of action. It is clear from the disclosure that the Applicants were in possession of compounds that reduce sympathetic nervous system activity and that one of skill in the art would know how to select and use a compound that affects the sympathetic nervous system to treat a patient with cachexia. The examiner's attention is specifically drawn to the large amount of data in the application as filed, with respect to a number of different compounds and underlying disorders, the statistical significance of the results, and the enclosed publications, any of which alone should be sufficient to rebut the rejection.

Rejection Under 35 U.S.C. § 102

Claims 1-4, 19, 29-31 and 41 were rejected under 35 U.S.C. § 102(b) as being anticipated by The RALES investigators Amer. J. Cardiol. 78:902-907 (1996) ("RALES"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The instant claims recite a method of treating **weight loss** due to an underlying disease, **not the disease itself.** RALES does not teach or suggest selecting patients with cachexia, nor does it disclose any sort of weight gain from the treatments. A patient with congestive heart failure (CHF) may develop cachexia, but by no means do all patients with CHF automatically

have cachexia. Page 35, for example, shows that there are cachectic CHF patients and non-cachectic CHF patients. Page 47, line 17 to page 48, line 5 discusses the proportion of CHF patients who have weight loss: 31.6% developed 7.5% weight loss during follow-up. Therefore, a treatment for cachexia is **not** the same as a treatment for the underlying disease. For example, aldosterone antagonist treatment is not limited to cachexia accompanying chronic heart failure- it can be also be used to treat cachexia accompanying other underlying diseases.

Inherency, which is the basis for the examiner's rejection, requires more than a mere possibility the claimed result will occur. It requires that there must be a reasonable prediction of the result. The fact that some patients may have experienced some weight gain during prior treatment is not the same as selecting those individuals in need of treatment for weight loss, administering an effective amount of a compound as claimed ***for an effective time to treat weight loss.***

Claim Objections

Claims 2, 36, 39, and 41 were objected to for citing non-elected inventions. As noted above, until the request for reconsideration is decided, these claims are properly pending.

Claims 36 and 39 have been cancelled. Applicants have not amended claims 2 and 41 to remove the non-elected species since a decision on the Applicants' Petition for Reconsideration of the Restriction Requirement is still pending. In addition, Applicants remind the Examiner that upon allowance of a generic or "linking" claim, the Applicants are entitled to consideration

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of claims to the non-elected species which are written in dependent form or otherwise include all the limitations of an allowed generic claim.

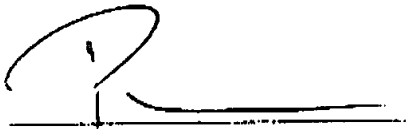
Drawing Objections

The drawings were objected to as failing to meet the requirements under 37 CFR § 1.84 (o).

Replacement drawings, Figures 1-4, are enclosed. Original Figure 1 is now Table A, and original Figures 2 to 5 are now Figures 1 to 4, respectively. The replacement drawings have been submitted in response to the Examiner's concerns with regard to legibility and visibility. No new matter has been added.

Allowance of claims 1-32, 41 and 46-47, as amended, is respectfully solicited.

Respectfully submitted,



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